

From the INTERNATIONAL SEARCHING AUTHORITY

**PCT**

To:

DORSEY & WHITNEY LLP  
Attn. Abelev, Gary  
250 Park Avenue  
New York NY 10177  
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT AND  
THE WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing  
(day/month/year)

26/05/2008

Applicant's or agent's file reference

188959/PCT

**FOR FURTHER ACTION**

See paragraphs 1 and 4 below

International application No.

PCT/US2008/051404

International filing date  
(day/month/year)

18/01/2008

Applicant

THE GENERAL HOSPITAL CORPORATION

1. ☒ The applicant is hereby notified that the International search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

**Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.  
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

**4. Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

**DOCKETED**

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Anne Witzig

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 188959/PCT	<b>FOR FURTHER ACTION</b> see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2008/051404	International filing date (day/month/year) 18/01/2008	(Earliest) Priority Date (day/month/year) 19/01/2007
Applicant THE GENERAL HOSPITAL CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of:



the international application in the language in which it was filed



a translation of the international application into \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

- b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6(b)(a)).
- c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

the text is approved as submitted by the applicant



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 3



as suggested by the applicant



as selected by this Authority, because the applicant failed to suggest a figure



as selected by this Authority, because this figure better characterizes the invention

- b. ☐ none of the figures is to be published with the abstract

A. CLASSIFICATION OF SUBJECT MATTER  
INV. G01N21/64 G01N33/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P;X	WO 2007/083138 A (PERKINELMER SINGAPORE PTE LTD [SG]; COURTNEY PATRICK [GB]; ORANGE PAUL) 26 July 2007 (2007-07-26) figures 5-7	1-22
X	US 6 297 018 B1 (FRENCH TODD E [US] ET AL) 2 October 2001 (2001-10-02) columns 9-10; figure 3	1-22
X	EP 0 617 286 A (WALLAC OY [FI]) 28 September 1994 (1994-09-28) figure 3	1-22
X	US 2004/072200 A1 (RIGLER RUDOLF [CH] ET AL) 15 April 2004 (2004-04-15) paragraphs [0026], [0027]	1-22

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*I\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

16 May 2008

Date of mailing of the international search report

26/05/2008

Name and mailing address of the ISA/  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Mason, William

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/108911 A1 (KLIMANT INGO [DE] ET AL) 12 June 2003 (2003-06-12) paragraphs [0023] - [0025] -----	1-22
A	WO 2006/059109 A (IC INNOVATIONS LTD [GB]; KLUG DAVID [GB]; DE MELLO ANDREW [GB]; TEMPLA) 8 June 2006 (2006-06-08) paragraph [0026] -----	1-22
A	US 2002/158211 A1 (GILLISPIE GREGORY [US]) 31 October 2002 (2002-10-31) figure 6 -----	1-22
A	US 5 955 737 A (HALLIDY WILLIAM H [US] ET AL) 21 September 1999 (1999-09-21) figure 8 -----	1-22

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2007083138	A	26-07-2007	NONE	
US 6297018	B1	02-10-2001	NONE	
EP 0617286	A	28-09-1994	DE 69422210 D1 DE 69422210 T2 ES 2139728 T3 FI 931198 A JP 6317593 A	27-01-2000 20-04-2000 16-02-2000 19-09-1994 15-11-1994
US 2004072200	A1	15-04-2004	AU 1603502 A WO 0238806 A2 EP 1409721 A2	21-05-2002 16-05-2002 21-04-2004
US 2003108911	A1	12-06-2003	DE 10137530 A1 EP 1281964 A2	13-02-2003 05-02-2003
WO 2006059109	A	08-06-2006	EP 1828747 A1	05-09-2007
US 2002158211	A1	31-10-2002	WO 02084267 A1 US 2004007675 A1	24-10-2002 15-01-2004
US 5955737	A	21-09-1999	NONE	

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

### FOR FURTHER ACTION

See paragraph 2 below

International application No.  
PCT/US2008/051404

International filing date (day/month/year)  
18.01.2008

Priority date (day/month/year)  
19.01.2007

International Patent Classification (IPC) or both national classification and IPC  
INV. G01N21/64 G01N33/58

Applicant  
THE GENERAL HOSPITAL CORPORATION

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Date of completion of  
this opinion

see form  
PCT/ISA/210

Authorized Officer

Mason, William

Telephone No. +49 89 2399-2623



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2008/051404

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:
  - ☒ the international application in the language in which it was filed
  - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ on paper
    - ☐ in electronic form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in electronic form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2008/051404

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	<u>4, 15</u>
	No: Claims	<u>1-3, 5-14, 16-22</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

Re Item V.

1. The present application relates to a method and apparatus for distinguishing first and second molecules having first and second luminescent characteristics wherein the characteristics comprise at least two different luminescent properties such as lifetime, excitation / emission wavelengths or anisotropy (polarisation) by determining information regarding the molecules as a function of the luminescent properties. In particular the claimed invention comprises distinguishing molecules by immobilising fluorophores thereto which have fluorescent properties such as spectral characteristics and lifetime which are both measured so that the combination of spectral and lifetime information can be used to resolve the two different fluorophores.

The following documents are referred to:

D1=WO2007083138; D2=US6297018; D6=WO2006059109.

2. CLARITY AND INTERPRETATION OF CLAIMS (ART. 6 PCT)

Independent claim 1 is directed to an apparatus whereas the dependent claims are introduced as "arrangements" - this inconsistency should be removed by rewording "arrangement" to "apparatus"

"First arrangement configured to receive an unpartitioned electro-magnetic radiation". This does not exclude e.g. subsequent spectral separation in the first arrangement even though the subsequent wording refers again to "unpartitioned electromagnetic radiation" since this is qualified by the wording "based on".

The wording "configured to" in claim 1 followed by a list of functions defines a result to be achieved since the skilled person is not familiar with such "black box" "first arrangement" which perform all of the functions of "receiving ...", "obtaining ..." and "measuring ..." as a single entity - this wording should be re-defined by listing individual functional features defining means for performing each of the separate

functions which would be familiar to the skilled person.

**3. PRIORITY**

Assuming the priority of the claimed invention is valid, D1=WO2007083138 is not comprised in the state of the art.

**4. PRIOR ART**

D2=US6297018 (Fig. 3; col 9, line 25 - col 10, lin 45) discloses methods and apparatus for detecting nucleic acid targets luminescence-based assays using i.a. luminescence polarization. In a first basic embodiment the spectral properties of the label would identify up to four nucleotides actually incorporated a nucleic acid sample.

According to another basic embodiment, lifetime methods may be used to distinguish luminescence signals even if the associated excitation and emission spectra are similar, two- to four-lifetime detection methods may be constructed that require only one excitation and one emission wavelength. For example, call a series of four luminescent labels with similar excitation and emission spectra but distinguishable luminescence lifetimes F1, F2, F3, and F4. Using the four dideoxy terminators, create the dye terminators ddATP-F1, ddTTP-F2, ddCTP-F3, and ddGTP-F4. The number of required labelled-nucleotides depends on the number of alleles corresponding to the polymorphism of interest. For example, if there are four alleles, each differing by a single nucleotide substitution (A, T, G, C), then a four-lifetime method is appropriate. Alternatively, if there are only three or two alleles, then a three-lifetime or two-lifetime method is appropriate, respectively. US6297018 continues with the following disclosure: "It also is possible to use COMBINATIONS of wavelength and lifetime discrimination to determine the incorporation of the four labelled nucleotides, if F1 through F4 differ from one another in COMBINATIONS of excitation/emission wavelengths and lifetimes that can be reliably distinguished from one another. Dyes can be distinguished by using wavelength and lifetime sequentially. For example, F1 through F3 could be distinguished from F4 by wavelength, and F1 through F3 could

be distinguished among themselves by lifetime. Dyes also can be distinguished by using wavelength and lifetime simultaneously. For example, F1 through F4 could be distinguished among themselves in a TWO-DIMENSIONAL space based on wavelength and lifetime. It may be more reliable to use both wavelength and lifetime than either alone, depending on the refinements in spectral and lifetime properties of dyes that are possible." In addition, US6297018 also discusses the use of the method in an imaging mode which would therefore detect the spatial distribution of light emanating from the sample as well as the fact that in the time domain the luminescence decays as a series of exponentials implicitly determined by measuring at a number of predetermined interval times so as to determine the "lifetime (inverse decay rate)".

US6297018 also discloses that luminophores may be used in a variety of luminescence assays, including fluorescence polarization (FP), fluorescence resonance energy transfer (FRET), and fluorescence recovery after photo bleaching (FRAP) - in FRET the information determined ascertains an association between a first and second molecule.

**5. NOVELTY**

In view of the interpretation of claims and the disclosure of D2=US6297018, claims 1-3, 5-14, 16-22 do not meet the requirement of novelty (Art. 33.2 PCT).

**6. INVENTIVE STEP**

The features of following further claims are disclosed in or evident from the prior art as indicated:

Claims 4, 15. Intrinsic (rather than) extrinsic luminescent characteristics used. See e.g. D6=WO2006059109 (paragraph 26).

Claims 4, 15 therefore do not meet the requirement of inventive step (Art. 33.3 PCT).

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	<p>In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT).</p> <p>If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).</p>
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003